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None declared.

Disease Modifying Therapy in Progressive Multiple Sclerosis：A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Review question / Objective: **The objective of this systematic review was to evaluate the efficacy and safety of disease-modifying therapies for progressive multiple sclerosis, especially the optimal choice of medication for different populations.**
Eligibility criteria: **Inclusion criteria :(1) study type :RCT; (2) Language restriction: available in English; (3) Subjects: patients ≥18 years of age diagnosed with progressive multiple sclerosis, whether with a primary progressive course or a secondary progressive course who met the 2017 McDonald diagnostic criteria; (4) Interventions: Disease modifying therapies including Ocrelizumab, Natalizumab, Rituximab, Laquinimod, Siponimod, Fingolimod, IFN-beta-1b, IFN-beta-1a, Glatiramer Acetate, Mitoxantrone, Dimethyl Fumarate; (5) control: placebo; (6) Outcomes: clinical outcomes including the expanded disability status scale (EDSS) and the number of patients with confirmed disease progression (CDP); the patients evaluated outcomes were the timed 25-foot walk (T25FW) and the 9-hole peg test (9HPT); magnetic resonance imaging (MRI) outcomes including change in the volume of lesions on T2 and the number of patients with new or newly enlarged lesions in T2; safety outcomes including adverse events (AEs) and serious adverse events (SAEs). Included RCTs were not required to include all the outcomes mentioned above.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 February 2023 and was last updated on 16 February 2023 (registration number INPLASY202320071).

INTRODUCTION

Review question / Objective: **The objective of this systematic review was to evaluate the efficacy and safety of disease-modifying therapies for progressive multiple sclerosis, especially the optimal choice of medication for different populations.**

Condition being studied: **Multiple sclerosis (MS) is a classic inflammatory disease of the central nervous system (CNS) that manifests as a chronic, inflammatory,**

demyelinating disease that causes primary demyelinating plaques or neurodegeneration mainly in the white and gray matter of the brain and spinal cord. More than 2.5 million people worldwide are affected by MS, and MS is now recognized as the leading cause of non-traumatic neurological disability in adolescents. At present, it is believed that the pathogenesis of multiple sclerosis is mainly caused by immune, genetic and environmental factors, but the ultimate cause is unknown, especially the mechanism driving the continuous progression of the disease is not clear. For relapsing remitting multiple sclerosis (RRMS), anti-inflammatory or immunosuppressive therapy can significantly benefit patients, reducing the severity and frequency of new demyelinating episodes. However, for the progressive multiple sclerosis (PMS), such as PPMS and SPMS, anti-inflammatory and immunotherapy have little effect. At present, the mainstream treatment of PMS is disease-modifying therapies (DMT), which can delay the progression of the disease and reduce the deterioration of the disease by oral or injection of DMT-related drugs. Now, more than 10 drugs have been included in DMT therapy, including: Ocrelizumab, Natalizumab, Rituximab (RTX), Laquinimod, Siponimod, Fingolimod, interferon-beta-1b (IFN-beta-1b), interferon-beta-1a (IFN-beta-1a), Glatiramer Acetate (GA), Mitoxantrone, Dimethyl Fumarate (DF). Meanwhile, new drugs are in the pipeline.

The primary objective of this meta-analysis was to compare the efficacy and safety of various agents in the DMT treatment of PMS. Because the longer the duration of PMS, the worse the recovery and the higher the mortality, we used expanded disability status scale (EDSS) and confirmed disability progression (CDP) to evaluate the efficacy of drug treatment for PMS. The results of confirmed worsening of at least 20% from baseline in the timed 25-foot walk test (T25FW), increase of 20% or more from baseline (on either hand) on the nine-hole peg test (9HPT) and magnetic resonance imaging (MRI) were used as the supplement of the therapeutic effect, and the adverse events of various drugs were sorted out as the prognosis to compare the advantages and disadvantages of various drugs. However, the current treatment effect on multiple sclerosis is still poor. Therefore, in order to provide evidence for clinicians, we pooled the data of previous randomized controlled trials and conducted a systematic review and network meta-analysis (NMA) to investigate the efficacy and safety of different drugs in DMT for the treatment of PMS.

METHODS

Search strategy: MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov were systematically searched to identify relevant studies published before January 31, 2023. The following search strategy was employed: (disease modifying therapy [Title/Abstract]) AND (multiple sclerosis [Title/Abstract]) for MEDLINE; “disease modifying therapy”/exp AND “multiple sclerosis”/exp for EMBASE; " disease modifying therapy" in Title Abstract Keyword AND "multiple sclerosis" in Title Abstract Keyword for Cochrane Library; “disease modifying therapy | multiple sclerosis” for ClinicalTrials.gov.

Participant or population: Patients ≥18 years of age diagnosed with progressive multiple sclerosis, whether with a primary progressive course or a secondary progressive course who met the 2017 McDonald diagnostic criteria.

Intervention: Disease modifying therapies including Ocrelizumab, Natalizumab, Rituximab, Laquinimod, Siponimod, Fingolimod, IFN-beta-1b, IFN-beta-1a, Glatiramer Acetate, Mitoxantrone, Dimethyl Fumarate.

Comparator: Placebo.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Inclusion criteria :(1) study type :RCT; (2) Language restriction: available in English; (3) Subjects: patients ≥18 years of age diagnosed with progressive multiple sclerosis, whether

with a primary progressive course or a secondary progressive course who met the 2017 McDonald diagnostic criteria; (4) Interventions: Disease modifying therapies including Ocrelizumab, Natalizumab, Rituximab, Laquinimod, Siponimod, Fingolimod, IFN-beta-1b, IFN-beta-1a, Glatiramer Acetate, Mitoxantrone, Dimethyl Fumarate; (5) control: placebo; (6) Outcomes: clinical outcomes including the expanded disability status scale (EDSS) and the number of patients with confirmed disease progression (CDP); the patients evaluated outcomes were the timed 25-foot walk (T25FW) and the 9-hole peg test (9HPT); magnetic resonance imaging (MRI) outcomes including change in the volume of lesions on T2 and the number of patients with new or newly enlarged lesions in T2; safety outcomes including adverse events (AEs) and serious adverse events (SAEs). Included RCTs were not required to include all the outcomes mentioned above.

Information sources: MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov were systematically searched to identify relevant studies. Additionally, the reference lists of RCTs, relevant systematic reviews and meta-analyses were also screened independently and manually to ensure a more comprehensive search.

Main outcome(s): Main outcomes including the expanded disability status scale (EDSS) and the number of patients with confirmed disease progression (CDP).

Additional outcome(s): Additional outcomes including the timed 25-foot walk (T25FW) and the 9-hole peg test (9HPT); magnetic resonance imaging (MRI) outcomes including change in the volume of lesions on T2 and the number of patients with new or newly enlarged lesions in T2; safety outcomes including adverse events (AEs) and serious adverse events (SAEs).

Quality assessment / Risk of bias analysis: A risk of bias plot was evaluated with Review Manager 5.3 software. The uniform criteria of the Cochrane collaboration were used to assess the risk of bias for RCTs, which included the following: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. Each bias criterion was classified as "low", "high", or "unclear". The assessment was carried out independently by two authors. Disagreements were settled by consulting with a third author.
The certainty of direct and indirect evidence of network meta-analyses were assessed using the Confidence in Network MetaAnalysis framework (CINeMA) according to the recommendations from the Grading of Recommendations, Assessment, Development, and Evaluation (i.e., "GRADE") Working Group. Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval and sample size), inconsistency and indirectness (study population), and risk of publication bias (funding sources), two authors independently classified the overall quality of evidence as high, moderate, low, or very low. Disagreements were also resolved through consultation with a third author.

Strategy of data synthesis: Network meta-analysis was performed for each outcome using R 3.5.2 software and gemtc R package. The Markov chain Monte Carlo methods involved four chains with over-dispersed initial values and Gibbs sampling based on 50,000 iterations after a burn-in phase of 20,000 iterations. We estimated summary risk ratio (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes with their 95% credible intervals (CI) (CI for Bayesian framework and confidence interval [CI] for frequentist setting). The chi-square q test and I2 statistic were also used to evaluate heterogeneity between trials in the network meta-analysis. To rank the performance of different DMT treatments and placebo in each outcome, the surface under curve ranking area (SUCRA) was created. For each outcome, a larger SUCRA value indicated a better rank for the intervention. The ranking probabilities were calculated as cumulative probabilities with each intervention being ranked. For all the

analyses, two tailed tests were performed and a P value < 0.05 was considered to be statistically significant.

Subgroup analysis: Not applicable.

Sensitivity analysis: We analyzed inconsistencies between direct and indirect sources of evidence to determine consistency. We examined the goodness of fit of the consistency and inconsistency models and estimated the difference between the direct and indirect estimates for one of the three comparisons in each closed loop produced by the three partial evaluation procedures, all of which are compared with each other.

Language restriction: Available in English.

Country(ies) involved: China.

Keywords: Progressive multiple sclerosis; disease modifying therapy; network meta-analysis; systematic review.

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